Allergic reactions to foods by inhalation in children

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ABSTRACT

This article focuses on hypersensitivity reactions after inhalation of food particles as primary cause for food allergy. This is an increasingly recognized problem in children. Reactions are commonly diagnosed in children who develop symptoms when the food is ingested. Some children tolerate the food when it is eaten but they experience reactions to airborne food particles such as peanut, cow's milk, and fish. The exposure can be trivial, as in mere smelling or being in the vicinity of the food. Usually, respiratory manifestations include rhinoconjunctivitis, coughing, wheezing, and asthma, but in some cases even anaphylaxis has been observed. Practical approaches concerning diagnosing clinical reactivity including skin tests, serum IgE antibodies, specific provocation tests, and management have been identified. Studies are warranted to establish the accuracy of diagnostic tests as well as incidence, prevalence, and natural history of food allergy through inhalation route.

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Hypersensitivity reactions to food commonly occur after ingestion of the food. Food may also behave as an airborne allergen and some patients develop clinical hypersensitivity reactions after inhalation of aerosolized food particles. These reactions are often serious and even life-threatening.

This article focuses on allergic reactions to foods induced by inhalation in pediatric age children. A search of the literature using the PubMed database was undertaken for articles in English published in the last 10 years. The literature search was undertaken in August 2013. The following search terms were used: food, allergy, inhalant, anaphylaxis, and asthma with and without filter; age, birth to 18 years. The search found 4423 references that were reviewed. Systematic reviews, meta-analysis, randomized-controlled trials, observational studies, and case reports were included. Relevant articles published before 2003 were either familiar to the authors or they were selected by searching the reference lists of identified articles. We also referenced nonsystematic reviews and studies in adults that were useful for the purpose of this article.

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EPIDEMIOLOGY

In childhood, prevalence of food allergy varied from 1 to 10%, being higher when diagnosis is based on parents' perceptions of food allergy.[1,2] Both prevalence figures and spectrum of food allergens differ considerably between geographical regions and are thought to reflect the discrepancy in diet between different nations. The prevalence of food allergies appears to be rising in industrialized countries, although reliable, population-based data are limited. According to the "hygiene hypothesis," this increase may be the result of low exposure to microbial antigens in early life that delays the development of the immune tolerance by limiting the Th2/Th1 switch or by a distinct genotype characterizing a more severe clinical subtype as in atopic dermatitis.[3]

There are sparse epidemiological data on the frequency of reaction to food particle inhalation in children with food allergy. An Internet-based survey showed that in 51 responders, median age of 7 years, with anaphylactic reactions to foods, most reactions (78%) occurred after ingestion, eight (16%) reactions occurred after exclusive skin contact, and three (5.9%) reactions occurred after exposure to aerosolized food.[4] A cohort of 512 children with milk/egg allergy were prospectively followed for a median of 36 months. A total of 1171 reactions to any food were reported; 14(1.2%) reactions were precipitated by inhalation of the food proteins.[5] In 1411 Canadian children with peanut allergy, the annual incidence rate of clinical reaction after accidental exposure to peanuts was

12.5%. Thirteen (4.8%) of 266 reactions occurred *via* inhalation of food particles.[6] In children allergic to seafoods, inhalation of seafood molecules precipitated ocular rhinitis in 16% of subjects.[7] Other authors have found that at their clinic ~5% of children with food allergy and asthma have bronchial symptoms after inhaling the relevant food.[8]

CLINICAL FEATURES

The diagnosis is based on history and objective assessment of the relationship between inhalation of food and onset of symptoms. In the majority of patients, inhalation of food particles induces respiratory symptoms, asthma, coughing, wheezing, and ocular rhinitis. In addition, skin manifestations such as urticaria or skin rashes and rarely anaphylaxis can occur.[9] Despite the suboptimal positive predictive value of skin-prick test or serum-specific IgE to food in general, specific IgE to the triggering inhalant food is commonly positive. The improvement of symptoms by avoiding the offending food offers a support for the diagnosis. A positive challenge to the food in question may be necessary to confirm the diagnosis.[10]A specific inhalation challenge should be the confirmatory test if it can be appropriately designed to avoid bias. Challenge test is time-consuming and not without risk. It is generally performed for research purposes and there is no consensus on the procedure that may be open[8]or, in selected cases, double blind placebo controlled.[11] The protocol should mirror the exposure that induced the reaction to the food.[8,11] Blood pressure should be monitored during the challenge.[12] Recently, exhaled nitric oxide[13,14] and markers in exhaled breath condensate[14,15] as noninvasive methods of investigating airway inflammation in asthma have been investigated. Even if their role in the diagnosis of reactions to food inhalation remains undetermined, they may be potentially useful.

Treatment is based on strict avoidance of exposure to aerosolized proteins of the offending food. Patients should understand that children may be exposed to airborne food proteins at school, restaurants and/or cafeterias, airplanes, fish markets, or grocery stores. At these places, the personnel should be educated on food allergy when possible. The presence of food proteins in medication administered *via* inhalation must be checked before administration. When the patient is asthmatic, a good control of symptoms should be achieved. A prophylactic treatment with long-acting antihistamine might be useful for mild reactions.[9] Patients or caregivers must always keep self-injectable epinephrine, antihistamines, steroids, and short-acting β_2-agonists to treat reactions.

ENVIRONMENTAL EXPOSURE

Aerosolized food particles have been detected in the air samples not only from a confined area[16] but also from outdoor environments such as a fish markets[17] or soybean unloading in the harbor.[18] Airborne food allergens are generated when the food is cooked, particularly boiled or steamed,[9] or manipulated, especially cutting or cleaning. Food processing is not always required to produce airborne food particles. Inhalation of peanuts has been shown to induce self-reported symptoms during commercial flights that provide peanut snacks.[19,20] Small amounts of airborne peanut proteins were measured after removing shells from roasted peanuts.[21] A 5-year-old boy who reacted to peanut odor developed wheezing when entering the classroom where the teacher had eaten peanuts.[22] In a 6-year-old school milk–allergic child, casein contained in chalk caused asthma and rhinoconjunctivitis at school.[23] An episodic epidemic of severe asthma attacks reported in Barcelona was caused by the inhalation of dust dispersed during the unloading of soybean at the port.[24] Overall, the question about characterization of aerosolized food allergen and differences between foods in producing airborne proteins remains unclear.

SENSITIZATION ROUTE

How primary sensitization to foods occurs is also a question. Reactions to inhaled food allergens generally develop in children who had IgE-mediated reactions after the ingestion of the offending food,[25] suggesting that sensitization to foods took place through the gastrointestinal mucosa or through the skin as shown by murine models.[26–28] In these cases an increased IgE response may be implicated in the onset of reaction to the aerosolized allergen. In this respect, it is noteworthy that in many patients, clinical reactions after inhalation of peanuts,[16] fish, or shellfish[24] were more severe than those induced by oral intake.

It has also been reported that in adults with occupational asthma, inhalation of food allergens might be considered a relevant route of primary sensitization.[29] At the workplace, inhalation of airborne food molecules from wheat,[30] cow's milk,[31–33] hen's eggs,[34] soybeans,[24] seafood,[35] and enzymes used in the cheese industry,[36] as well as many vegetables, fruits, spices, mushrooms, additives, and contaminants,[16] trigger allergic reactions. Levels of exposure at the workplace are directly related to the development of symptoms.[35] Likewise, in allergic asthma, skin-prick tests or serum IgE to the offending food are usually positive and the inflammatory infiltrate is mainly eosinophilic. However, presence of neutrophils in the absence of eosinophils in sputum does not exclude occupational asthma, suggesting that a specific inflammatory mechanism may be implicated.[37,38]Along this line, a clinical hyper-

Table 1 **List of foods eliciting clinical reaction by inhalation in childhood**

Food	Patient No.	Food	Patient No.
Bean[60,68]	2	Peanut[19,22,39,50,54]	>500 (the exact no. is not available)
Buckwheat[8,73,74]	10	Poppy seed[83]	1
Chickpea[8,56]	33	Potato[82]	1
Cow's milk[31,33,78]	3 adolescents and 13 children	Rice[70]	1
Fish[7,8,28]	53	Sesame[84]	1
Lentil[56–61]	51	Lupine[69]	1

sensitivity reaction to aerosolized food proteins such as peanuts[39] and shrimp[22] occur in children who had no history of previously ingesting the same foods. Moreover, in some children foods can induce clinical reactions by inhalation route while they are tolerated when ingested.[11] Some explanations may be offered for this latter finding. Patients may be sensitized to molecular allergens that differ from those eliciting allergic reactions by the ingestion route, as it has been observed in some patients with work-related asthma.[35] It may be the result of a production of specific IgE limited at the airways.[40] Another possibility is that food protein allergenicity may be reduced by processing or gastric digestion,[41] leading to the loss of their capacity to induce allergic reactions while intact allergens may elicit reactions in the airways.

FOODS

All foods may potentially induce clinical symptoms when they are inhaled. There are no epidemiological studies on the relative frequency of foods eliciting hypersensitivity by inhalation. Interestingly, Roberts *et al.*[8] described that 12 children with IgE-mediated food allergies referred to hospital clinic had an history of asthma when exposed to the relevant food allergens while they were cooking. Nine children underwent inhalation food challenge. Positive challenges were seen with fish ($n = 3$), chickpea ($n = 1$), and buckwheat ($n = 1$) in five children. The more commonly reported inhaled food allergens in children are seafood, legumes, peanut, tree nut, and cow's milk (Table 1).

Seafood

Fish is a common cause of food allergy.[1,2,42] In an Australian cohort of children with seafood allergy, 26 (16%) of 167 children experienced ocular or upper respiratory symptoms (rhinorrhea and nasal pruritus) on exposure to seafood vapors.[7] A study from Spain[28] reported that 21 of 197 children diagnosed with IgE-mediated fish hypersensitivity experienced allergic reactions on casual inhalation of fish odors or fumes. After diagnosis, all of these patients were placed on a strict fish avoidance diet. During the diet, patients developed allergic reactions after incidental inhalation of fish particles. Clinical manifestations through inhalation were respiratory, mainly wheezing, in 12 patients and cutaneous, mainly urticaria, in 9 patients. Nineteen of 21 patients reported three or more episodes after exposure to aerosolized fish. In most cases, these episodes occurred at home when other people were eating fish.

Parvalbumins are the major allergens and are responsible of cross-reactivity among different fish species.[43] They are involved in allergic reactions after ingestion as well as inhalation.[44] Other fish allergens of importance through the inhalational route include glyceraldehyde-3-phosphate dehydrogenase in a murine model.[45]

Several cases of children who had anaphylaxis after inhaling shellfish have been reported.[22,46] The major shellfish allergens are tropomyosins. They are responsible for cross-sensitization between crustaceans and, to a lesser extent, between crustaceans and molluscs.[47] Other allergenic proteins of shellfish are arginine kinase, myosin light chain, sarcoplasmic binding protein, and parasites including ciguatera and *Anisakis*.[48] No cross-reactivity has been indicated between crustacean or mollusc allergens and fish allergens.

Peanuts and Tree Nuts

Although ingestion of peanut and tree nuts can provoke severe reactions, the importance of exposure through inhalation is unclear.

Airborne exposure seems to rarely provoke first reaction to peanut or tree nuts. A rate of 1% of cases to peanuts and 3% to tree nut was found by a questionnaire study[49] on subjects who were mostly children; 89% aged 0–18 years, included 4685 patients with allergy to peanuts and 1667 allergic to tree nuts.

Most concerns about allergic reactions to aerosolized peanuts or nuts are the environment where they are commonly eaten such as schools and commercial flights. Sicherer *et al.*[50] investigated 4586 subjects with allergic reaction to tree nuts and/or peanuts by telephone questionnaire. Parents reported that 750 (16%) children reacted to food at school or day care. Reactions were reported by possible inhalation in 16% of cases. Concomitant ingestion/skin contact of peanuts

could be ruled out only in four episodes. In these episodes, the trigger was peanut butter and symptoms were ocular rhinitis, hives, and wheezing. In patients who had adverse reactions to peanuts aboard commercial flights, the reaction was self-reported to be triggered by inhalation in 33% of cases.[51] In the majority of patients, the symptoms were rhinorrhea and wheezing; one-half of them had a history of asthma. No anaphylaxis was reported. In a more recent telephone survey, Comstock *et al.*[20] reported on reactions to peanuts and tree nuts in 41 patients (68% had history of asthma) during flights, 58% of which were by inhalation. The reactions to peanuts were about four times more than tree nuts (73% versus 18%), probably because of more common peanut distribution. Many of the reactions by inhalation were classified as severe, although none were anaphylactic. Although 32 of these patients had been previously instructed to carry self-injectable epinephrine, only 12 (38%) had it with them on the flight. Greenhawt *et al.*[52] studied by questionnaire 150 subjects who had an in-flight reaction to peanuts or tree nuts. Anaphylaxis was reported in 50 subjects. Other symptoms were, in most cases, cutaneous, with itching and hives, rather than respiratory and gastrointestinal. Reported routes of exposure included ingestion,15.7%; inhalation, 48.6%; skin contact, 27.9%; and unknown, 7.8%. The responsible foods were peanuts, 64.1%; tree nuts, 16.9%; both peanuts and tree nuts, 4.7%; and 14.3% were peanuts, tree nuts, or both.

The concentration of airborne peanut protein that is necessary to elicit an indoor clinical allergic reaction is unknown.[21,53] Simonte *et al.*[54] investigated a laboratory procedure to imitate the casual exposure to peanut butter. They studied 30 highly sensitive children with peanut allergy; 11 had a history of inhalation reaction to peanuts and 13 had a contact reaction. Children underwent double-blind, placebo-controlled, randomized exposures to peanut butter with skin contact and inhalation. No child had reactions on inhalation challenge. They concluded that exposure to the odor of peanuts may not be sufficient to provoke reactions. The issue about peanuts, in particular, has raised great controversy and heated debates in the United States regarding the appropriateness of demanding elimination of peanuts from schools.[55]

Legumes

Legumes, such as peanuts, soy, lentils, chickpeas, lupine, and green beans, are among the five classes of food mainly responsible for IgE-mediated allergic reactions.[56–59]

Lentils. Very few patients in the literature who have experienced anaphylaxis by lentil inhalation during childhood have been reported. Kalogeromitros *et al.*[57] described a child with repeated anaphylactic reactions related to lentils after ingestion of cooked lentils and one episode after inhalation exposure to cooking lentil soup. Pascual *et al.*[60] described 3 of 22 children with clinical hypersensitivity to lentils had symptoms when they were exposed to steam from cooked lentils. An 8-year-old boy with a history of anaphylaxis after intake of lentils developed anaphylaxis after inhalation of steam from boiling lentils. Although he had positive serum-specific IgE for peanuts and soybeans, he could eat them without any allergic reaction.[11]

Leonardi *et al.*[61] described the first case report of anaphylaxis to aerosolized lentil particles in a 22-month-old child with urticaria and anaphylaxis due to inhalation of cooked lentils vapors. She was already on lentil exclusion diet from the age of 9 months when she presented with her first episode of angioedema and laryngeal obstruction due to ingestion of lentils.

The proteins with allergenic properties more frequently responsible for reactions are "vicilin" proteins.[62] Recently, it has been suggested as a possible pathogenic role for Bruchus lentis, a lentil pest, as an agent of allergic reactions caused by lentils, both after ingestion and vapor inhalation.[63]

Sanchez-Monge *et al.*[64] characterized two different types of allergens from boiled lentils. Len c 1, corresponds to γ-vicilin subunits, and Len c 2 corresponds to seed-specific biotinylated protein. Vereda *et al.*[65] recently identified the IgE-binding epitopes of Len c. Serological cross-reactivity among legumes is known to be frequent. In all of the boiled legume extracts of lentil, chickpeas, and peas, a protein band at ~50 kDa with intense specific IgE binding has been described.[66] It was also shown that several immunoreactive proteins still remained in lentils and chickpeas even after autoclaving.[67]

Chickpeas, Green Beans, and White Beans. One investigation described three children who develop urticaria, oral allergy syndrome, and allergic rhinitis after exposure to steam from cooked chickpeas and green beans.[60] Alonso *et al.*[68] described the case of a 7-year-old Spanish child who suffered from two episodes of angioedema related to white beans. The first episode occurred after ingestion of this legume. Subsequently, he presented with angioedema after inhalation of vapor from cooked white beans.

Lupine. Lupine flour is an excellent source of proteins and is used in biscuits, pasta, sauce, dietetic products sold as milk, and soy substitutes. The seeds are usually served with aperitifs. An 8-year-old asthmatic child, allergic to peanuts, had an asthma attack while playing with his brother, who had been eating lupine seeds as a snack.[69] He had a positive skin-prick tests and serum-

specific IgE antibodies to *Lupinus albus* extract. The patient had asthma 5 minutes after manipulation of the lupine seeds. Lupine seed should be considered a potential etiologic agent not only by ingestion but also by inhalation in patients allergic to peanuts.

Cereal Grain

The reactions to rice, wheat, and buckwheat usually occurs by ingestion but also can occur by inhalation in occupational or unexpected exposure.

Rice

An 11-year-old boy was reported to develop anaphylaxis, while his mother was cooking rice. He was able to consume rice without any symptoms, but inhalation challenge with rice induced anaphylaxis.[11] Another article described a 9-year-old girl who presented with urticaria/angioedema while she was in the kitchen where her mother was sorting rice. Her parents said that she avoided eating foods containing rice for the last 3 years. She had immediate nausea, abdominal pain, and diarrhea after ingestion of rice.[70]

In rice allergy, proteins with molecular masses of 14–16, 26, 33, and 56 kDa seem to be potentially allergenic, and the 33-kDa allergen, designated Glb33, is considered an important allergen in boiling rice vapor.[71] Lipid transfer protein may play a role in inducing reaction to rice by inhalation.[72]

Buckwheat

There are several case reports on inhaled buckwheat hypersensitivity.[8] Many Korean children traditionally use buckwheat chaff-stuffed pillows (BCP) contaminated with buckwheat flour during the process of pilling. Lee *et al.*[73] described three children whose nocturnal asthmatic symptoms improved during 7 days of BCP elimination, and asthmatic responses were observed by bronchial provocation tests with homemade buckwheat extract. All three children showed positive skin reactions and serum IgE antibodies to buckwheat. Matsumura *et al.*[74] reported six cases of Japanese children with asthma in which removal of BCP led to resolution of symptoms.

Wheat

Wheat is associated with IgE-mediated (wheat allergy) and non–IgE-mediated (celiac disease) symptoms.[75] In children wheat is one of the more frequent foods responsible for allergy by ingestion and the prevalence of wheat hypersensitivity is 0.3–0.5% among children aged 0–14 years.[76] Sensitization by inhalation to wheat has been described in adults and is responsible for asthma (bakers' asthma) and rhinitis.[77] Interestingly, patients with baker's asthma typically eat wheat products without symptoms. To the best of our knowledge, there is no evidence that children had allergic reactions after wheat inhalation.

Cow's Milk

Severe reactions to aerosolized milk protein have been reported.[23] A 18-year- old girl suffering from asthma and cow's milk allergy from infancy had fatal anaphylaxis when she entered a dairy shop.[78] Some formulations of inhaled medications contain lactose that generally does not induce reaction.[79] However, an 8-year-old boy with milk allergy and persistent asthma had anaphylactic reactions to milk protein contaminating lactose contained in fluticasone/salmeterol dry-powder inhaler. Variability of contamination from lot-to-lot is unpredictable. Therefore, lactose-containing dry-powder inhalers should be prudently used in patients with severe milk allergy.[80]

There is a need for studies on the tolerance of cow's milk substitutes[81] in children who reacted to cow's milk inhalation.

Other Foods

In an 8-year-old girl anaphylaxis occurred while potatoes were being boiled at home.[82] One article described a 16-year-old boy who developed erythema, angioedema, conjunctivitis, and dyspnea after the inhalation of poppy seed.[83] A 7-year-old girl presented recurrent episodes of wheezing and dyspnea after sesame inhalation.[84] In adults, there are reports highlighting reactions to some other foods such as hen's eggs and carrots by inhalation route. Inhalation type I hypersensitivity to hen's eggs may be associated with allergy to ingested eggs.[85] Airborne carrot allergens[86] have been found to induce asthma in patients who did not have a previous birch pollen allergy. Chicken particles contained in hot dog vapor triggered asthma attacks.[87]

CONCLUSIONS

The current literature primarily consists of observational studies, case reports, or case series of children in which the diagnosis of reactions to aerosolized food particles was frequently not based on objective means, such as inhalation challenge. Therefore, large controlled population-based studies are warranted to establish the accuracy of diagnostic tests as well as incidence, prevalence, and natural history of food allergy through inhalation route. Such studies would also be useful for defining needs for public health care service, especially if reactions due to food particle inhalation are frequent, as adult asthma caused by work environment.[88]

In clinical practice, reactions to airborne food protein should be suspected and can be severe and should be promptly recognized. The identification of the offend-

ing food is necessary to take actions for avoidance of exposure. Because about two-thirds of patients who had severe reactions to food inhalation had asthma, it would be appropriate to optimize the control of asthma in food-allergic patients. In addition, an effective preventive treatment and the best strategies for successfully achieving an education of children and caregivers are warranted to improve the quality of life of patients at risk of reactions to inhaled food proteins.

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